REMARKS/ARGUMENTS

Before responding to the Office Action, Applicants would like to thank the Examiner for the comprehensive interview she granted to Applicants' attorney and the constructive discussion held with respect to the present and related applications.

Applicants will respond to the various items in the office action in the order they are presented.

Claim Rejections - 35 USC § 101

The Examiner has rejected claims 1-10 under 35 USC § 101 "...because the claimed invention is directed to non-statutory subject matter." The Examiner did not find Applicants' prior arguments that the methods produced a concrete, tangible, and useful result persuasive.

The Examiner highlighted three particular points. First the Examiner states that:

"What the claimed methods do is generate data-based representations which simulate potential conformations of non-existing molecules."

Applicants respectfully disagree with the Examiner's characterization. The topomeric alignment method generates a standardized conformation of side chains that are derived from known reactants. The problem presented in the prior art was how to compare the shape of side chains derived from reactants since such side chains could assume a multitude of possible conformations. The solution taught by the present invention was the creation of a topomeric/rule based alignment procedure which aligned all side chains according to a standardized method. Since the side chains were now aligned by the same method (into the

topomeric alignment), the shapes of the side chains could now be meaningfully compared. This comparison of topomerically aligned side chains was found to be useful even if the topomeric alignment placed the atoms of a side chain into a conformation that they would not assume in a native environment. Applicants respectfully submit that the topomeric alignment method thus produces a concrete, tangible, and useful result.

Second, the Examiner states:

"The claims which end with COMFA steric field determinations are similarly non-statutory, as this calculation (the COMFA steric field) is a manipulation of data to an end which is not concrete, tangible and useful."

Applicants respectfully disagree with the Examiner's characterization. The calculation of the steric fields of a topomerically aligned side chain produces a molecular structural descriptor representative of the shape of the side chain which descriptor has been validated by methods taught in the specification. The molecular structural descriptor values for each side chain constitute a unique representation of the shape of that side chain that can be used to meaningfully compare the shape of that side chain to the shape of other side chains. Applicants respectfully submit that the field values about a topomerically aligned side chain thus produce a concrete, tangible, and useful result; namely a valid molecular structural descriptor of the shape of that side chain.

Third, the Examiner states:

"The claims that end with calculating field differences are also not concrete tangible and useful, as it is not set forth in the claim what one is to do with that particular

number/calculation, or what the difference value means."

Applicants respectfully disagree with the Examiner's characterization. The specification teaches that the field differences are reflective of the similarity or dissimilarity of the shape of the side chains. That is, comparison of the relative similarity of the side chains may be made by calculating the field differences between topomerically aligned side chains.

Applicants believe that the claims as presented in the Response to the first Office Action are statutory for the reasons set forth above. In order to more particularly point out and distinctly claim the subject matter that Applicants regard as their invention, Applicants have amended the claims. Consistent with the arguments presented above, Applicants have amended claims 1, 3, and 7. First, the claims now refer to generating a "*standardized*" conformation to emphasize that it is a single uniform conformation that is generated for each side chain.

Second, to eliminate any ambiguity, the claims have been amended to recite that it is the "*molecular side chains derived from reactant molecules*" that are being treated. The specification teaches that reactants (after removal of an atom or atoms) in a chemical reaction can be viewed as having a bond that is used to attach the remaining part of the reactant (the side chain) in the synthesis. The topomeric alignment procedure starts with placement of that bond onto a three dimensional grid. To be consistent, claims 2, 5, and 9 that referred to "fragments" have been canceled. As noted by the Examiner later in the Office Action, the specification used the word "fragments" in a couple different ways. The intended use in the canceled claims was to refer to the side chains derived from reactants. This was how the term was used in the specification during the discussion of the topomeric alignment, and Applicants

submit such use in the claims would be clearly understood by those skilled in the art.

Third, the claims have been amended to note that the molecular structural descriptor is used "*to determine similarity of shape*" and, in particular, that "*smaller field differences reflect greater similarity of shape.*"

Applicants respectfully submit that for the reasons cited above, the claims both prior to and after amendment are statutory, and Applicants respectfully request the Examiner to remove the 35 U.S.C. 101 rejections.

Claim Rejections - 35 USC § 112

The Examiner has rejected claims 1-10: "... under 35 USC § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." The Examiner states that:

> "Applicant argues that the idea of a "representative structure" is described in the specification. However, the metes and bounds of the claims reciting this term are still unclear. Applicant further argues about how the claims teach away from the prior art, however, this does not address the issue of indefiniteness. Each of claims 1-10 recite the term "representative structure." The steps of the claims do not indicate how a representative structure is generated, and identified. It would appear that the application of the topomeric alignment rules to one or more reactants would result in the generation of a number of differing potential conformations for each molecule. How does one pick what is "representative" out of those structures that are generated? Are all the generated

structures considered representative? Or is it a subset of those generated. What are the rules guiding the selection of the subset?"

Applicants' attorney and the Examiner discussed these concerns of the Examiner during the interview, and Applicants' attorney believes that the Examiner now understands that the application of the topomeric alignment rule to each side chain (derived from each reactant) generates only one standardized three dimensional conformation for each side chain. It is this topomeric conformation of each side chain which is representative of that particular side chain and which can be used to compare the shapes of one side chain to another. Applicants also incorporate their remarks made above in response to the 101 rejection with respect to the representativeness of the topomeric conformation. Applicants also submit that the amendment to include the term "standardized" further clarifies the fact that there is only one representative (standardized) conformation for each side chain. Applicants respectfully submit that the metes and bounds of the claim are clear and that the claims are definite.

The Examiner states that:

"The claims recite the term "fragment" which is not clearly defined in the specification, and it is not clear how Applicant intends the term to be interpreted."

Applicants have addressed the Examiner's concerns with the use of the term "fragment" in response to the 101 rejection and have canceled claims incorporating that term. However, as stated earlier, Applicants believe that a person reasonably skilled in the art (a computational chemist) would clearly understand that Applicants were referring to the side chains derived from the reactants as illustrated in the example of a topomeric alignment in the specification

and in the discussion of Figure 11.

The Examiner states that:

"In claims 7-10 it is unclear how the steps of the method meet the limitation in the preamble for "applying a molecular structural descriptor. Claim 7 ends with the calculation of field differences between all pairs of reactants. This does not seem to be the same goal. Claim 9 has a similar problem. Also, there is no clear step where any molecular structural descriptor is applied (other than possibly adding the hydrogen bonding fields). Structures generated by applying topomeric rules (which do not appear to be the same as a molecular structural descriptor), fields are determined, and differences are calculated."

Applicants respectfully disagree with the Examiner and incorporate their comments above in response to the 101 rejection. Applicants submit that the amendments further clarify the methods claimed. Claims 1 and 11 claim methods of generating a standardized representative three dimensional conformation using topomeric alignment. Claims 3 and 12 characterize the three dimensional shape of the representative conformations by calculating associated steric field values. These claims recited the method of defining the molecular structural descriptor. Claims 7 and 14 use the molecular structural descriptor (field values about topomerically aligned side chains) to compare the shapes of the side chains. Applicants submit that the amended claims are definite and meet the requirements of 35 U.S.C. §112, second paragraph. Accordingly, Applicants respectfully request that the Examiner remove the cited rejections.

Claim Rejections - 35 USC § 102(b)

The Examiner has rejected claims 1-10 "...under 35 U.S.C. 102(b) as being anticipated by Cramer, III et al. (USP 5,307,287 - of record in 08/592132). In particular the Examiner states:

> "...The claims as written do not require small pieces of a molecule. A "reactant molecule" is not an exclusion of a protein, and the indefiniteness of the term "fragment" has been discussed above. The term "reactant molecule" does not appear to be specifically defined in the specification, and, given its broadest reasonable interpretation, could be anything which reacts. Further, the claim does not exclude alignment against any particular conformer, as there are no specific topomeric alignment rules set forth in the claim. They are left to one of skill in the art to "define" in step (a) of the claimed methods. As set forth in the patent, the methods allow the user to see the areas of molecular shape most important to activity highlighted on the screen. This is generation of representative 3D conformations as required by claims 1-2. This also is a "characterization" of a 3D structure as required by claims 3-6. This is also the application of a structural descriptor as required by claims 7-10.

Applicants respectfully disagree with the Examiner's statement. Most importantly, each claim requires a topomeric alignment. There is no topomeric alignment in the Cramer reference. As taught in the specification, a topomeric alignment is rule based - that is, the atoms of the side chain are moved about (torsions adjusted) in accordance with a rule irrespective of whether the final structure is energetically reasonable or assumes a recognizable

native conformation. Applicants teach one particular set of topomeric alignment rules, but the specification also teaches that, once it is appreciated that topomeric alignments work, other rules may be constructed. Further, in the present application whole molecules are not aligned. Cramer, on the other hand, aligns whole molecules to each other and does not use a rule based alignment. Applicants submit that on this basis alone, Cramer can not anticipate the present invention.

It is unclear to Applicants how the Examiner equates viewing "areas of molecular shape [of whole molecules in Cramer] most important to activity highlighted on the screen" to the "generation of representative 3D conformations in claims 1-2" where the representative conformations are the topomeric conformations of constituent parts of molecules. CoMFA does not treat reactants (side chains) but rather deals with entire molecules. CoMFA alignment procedures, on the other hand, start by (sometimes arbitrarily) choosing one conformation of a first molecule (in the series of molecules all having measurable activity at the same receptor) and then aligning the remaining molecules in the series to the first molecule using various methods discussed in the CoMFA patent. Applicants believe that this misunderstanding must result from of what is meant by a "representative" conformation and that the misunderstanding has been clarified by the comments presented earlier in this Response. Similarly, the "characterizing" of claims 3-6 (now claims 3 and 12) refers to the generation of a molecular structural descriptor by generating the steric field values for each topomerically aligned side chain. Finally, Applicants do not understand how the Examiner equates viewing areas of molecular shape most important to activity as equivalent to the application of a structural

descriptor in claims 7-10 (now claims 7 and 14). Applicants respectfully submit that any ambiguity perceived by the Examiner has been eliminated by the amendments to the claims. Applicants also incorporate herein their remarks to the rejection in view of Cramer provided in the Response to the first Office Action. Applicants respectfully submit that they have overcome the grounds for the 35 U.S.C. §102(b) rejections, and request that the Examiner remove the rejections.

Claim Rejections - Double Patenting

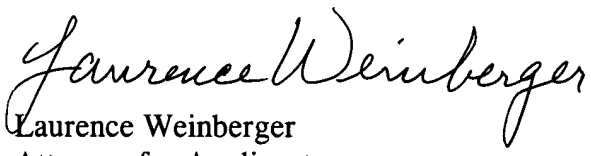
The Examiner has rejected claims 1-10: "...under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims of U.S. Patent No. 6,185,506." Applicants acknowledge this rejection and will timely file a terminal disclaimer once claims in the present application have otherwise been allowed.

No additional claim fees are due since fees for 10 total and 6 independent claims have been paid, and after amendment, there still remain 10 total and 6 independent claims.

Applicants submit that they have adequately addressed all grounds for rejection raised by the Examiner and respectfully request that a timely Notice of Allowance be issued in this case.

June 2, 2004

Respectfully submitted,



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